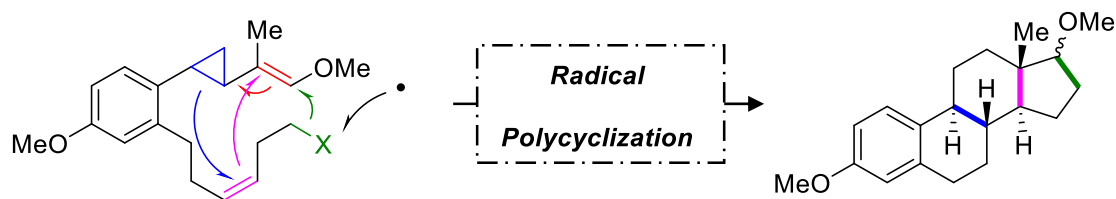


Radical Polycyclizations in the Synthesis of Heterocyclic Natural Products



Dan Forster

LSPN - Seminar

- Introduction
- Polycyclization cascades
 - C-centered radical initiated cascades
 - aldehydes
 - alkyl
 - alkenes
 - alkynes
 - N-centered radicals
 - N-aminyl radical
 - N-amidyl radical

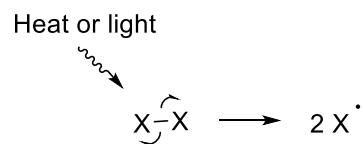
Why radical polycyclizations ?

Cascade polycyclization reactions => huge interest to shortly access complex frameworks

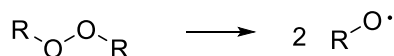
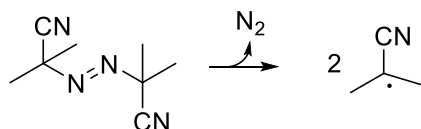
- Pericyclic reactions (electrocyclizations, cycloadditions, ..)
 - Very elegant, robust, complex structures can be obtained from a single transformation
 - Substrates must be carefully designed (matched/mismatched orbitals)
- Ionic cascades (cationic, anionic)
 - Present in biosynthetic pathways, nature's choice, well implemented
 - Difficult to control due to many possible rearrangements/shifts (carbocations), low functional group tolerance
- Radical cascades
 - Very reactive, extraordinarily short access to complex frameworks from simple starting materials

Radical generation

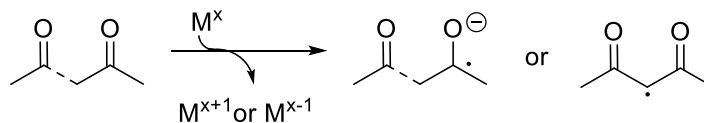
Homolysis



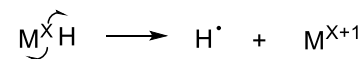
example :



Homolytic cleavage of weak,
non polarized bonds

Single-Electron
Reduction / C-H bond oxidation

Electron addition on polarized
bonds or metal oxidation of
activated C-H bonds

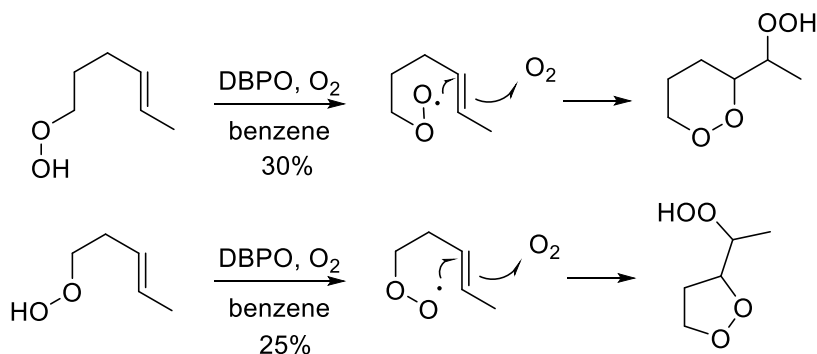
Metal mediated hydrogen
atom transfer

M = Mn, Fe, Co, Sn

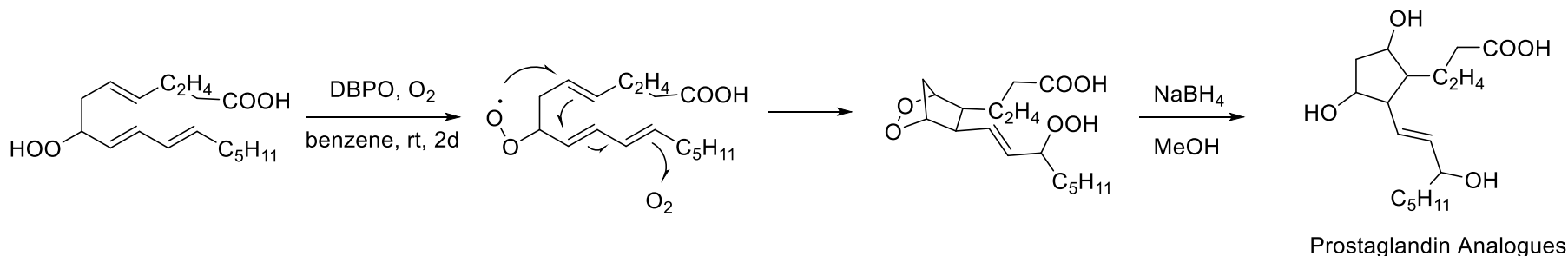
“Homolytic” cleavage of transition
metal hydrides generating highly
reactive hydrogen radical species

Once generated, radicals tend to propagate
=> well suited for cascade reactions to rapidly access complex frameworks.

Pioneering work : Porter (1970s) : peroxide initiated cascades for prostaglandins synthesis

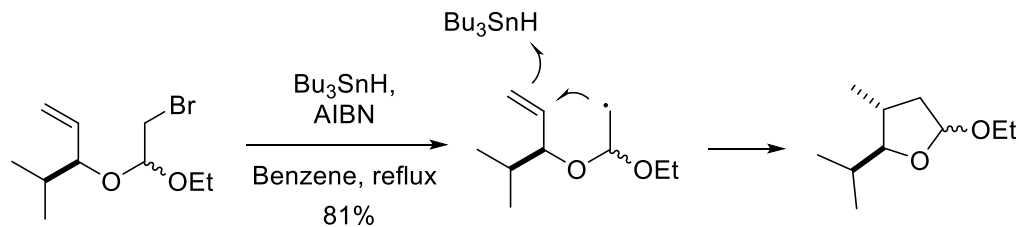


Observations in peroxy radicals cyclization, which were further used for the synthesis of prostaglandins analogues



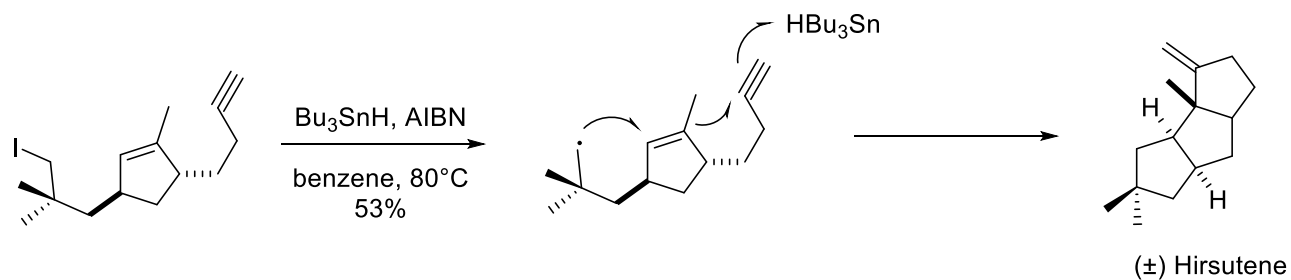
Porter, *J. Am. Chem. Soc.* **1975**, *97*, 1281; *J. Org. Chem.* **1975**, *40*, 3614

Pioneering work : Ueno-Stork 1980s : halo-abstraction and substrate design for regiocontrolled radical cascades



Ueno, *J. Am. Chem. Soc.* **1982**, *104*, 5564; Stork, *J. Am. Chem. Soc.* **1983**, *105*, 3471

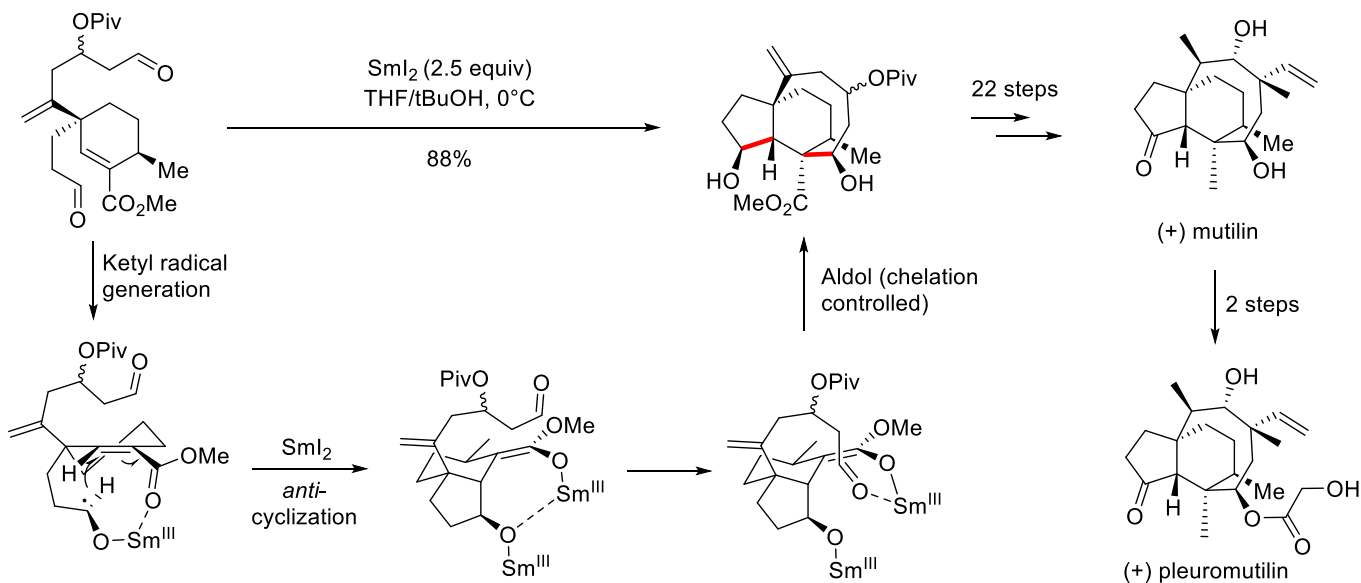
Pioneering work : Curran 1980s : Total synthesis of Hirsutene employing radical polycyclization



First radical polycyclization in the context of total synthesis

- Intro – radical generation
- Polycyclization cascades
 - C-centered radical initiated cascades
 - aldehydes / ketones
 - alkyl
 - alkenes
 - alkynes
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 - N-aminyl radical
 - N-amidyl radical

Sm(II) used for generation of ketyl radical via single electron transfer (SET)



Chelating effect of the ester on the Sm(III) induces :

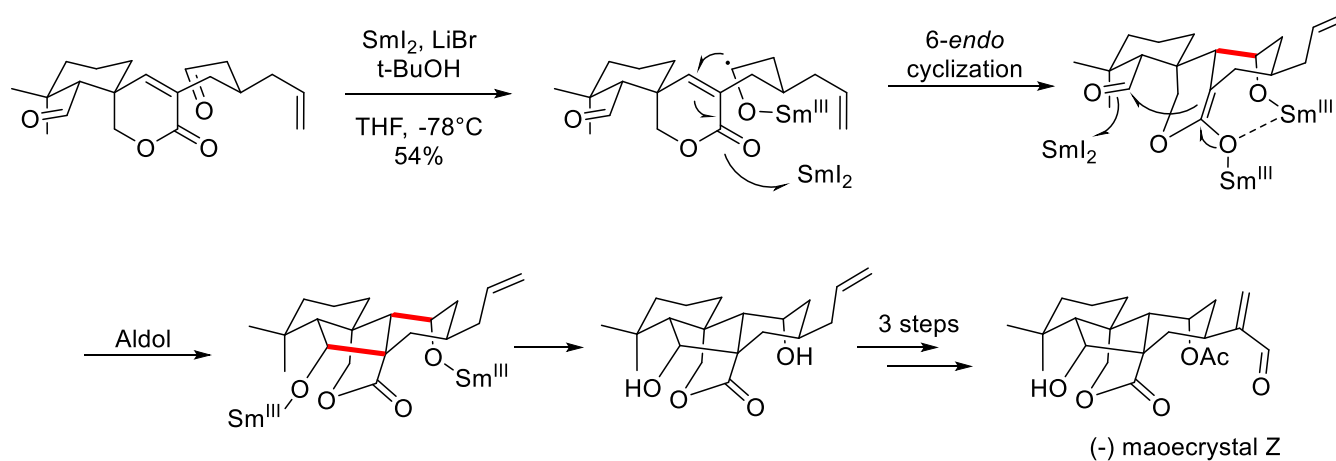
- Selective aldehyde reduction
- High diastereoselectivity

Procter, *Chem. Eur. J.* **2013**, *19*, 6718

Initial discory of SmI₂ as one electron reducing agent : Kagan, *J. Am. Chem. Soc.* **1980**, *102*, 2693–2698

C-Centered radical : aldehyde

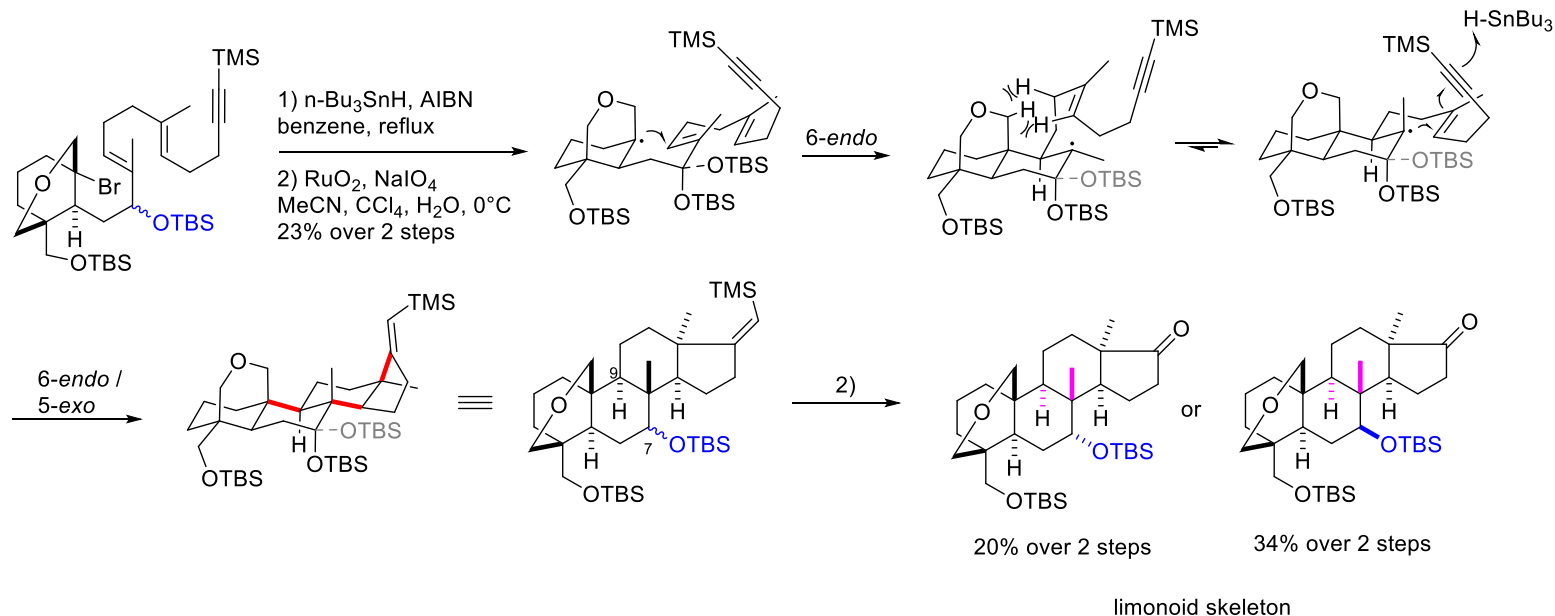
Sm(II) used for generation of ketyl radical via single electron transfer (SET)



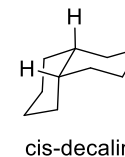
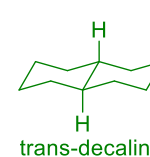
Chelating effect induces again high diastereoselectivity (single diastereomer)
Least hindered aldehyde reacts first

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Sn radical used for halo-abstraction to generate stable tertiary C-centered radical



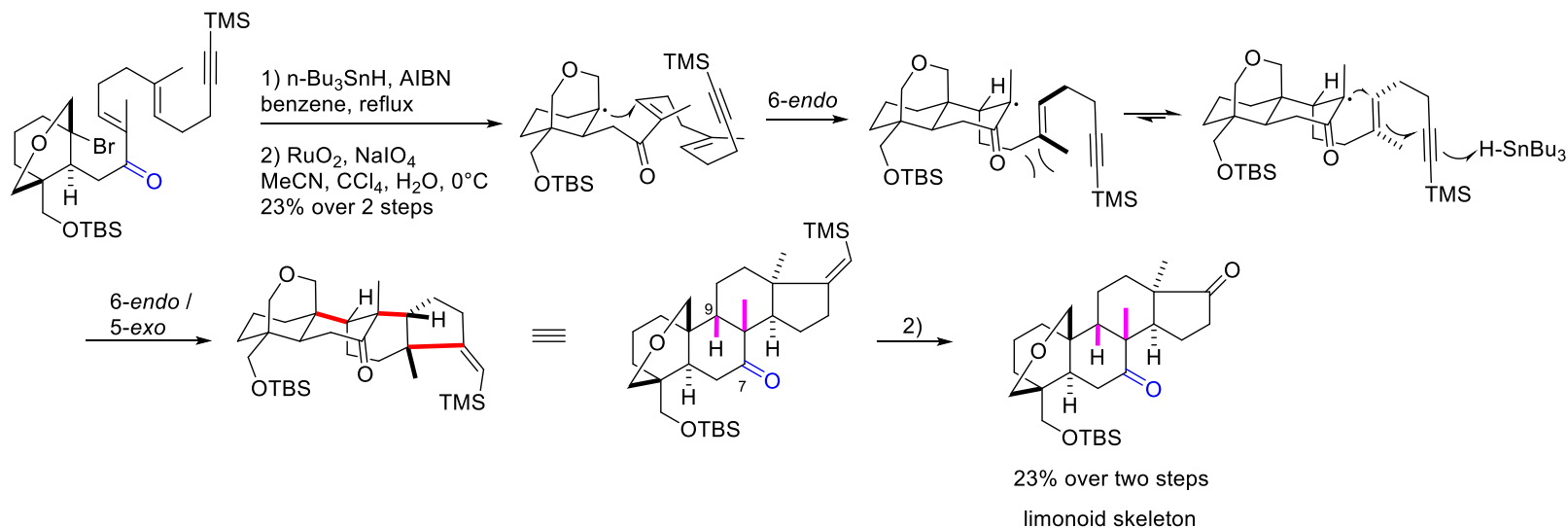
- First 6-endo occurs from top face of the pseudo-chair form due to sp^3 hybridized carbon atom next to double bond (C-OTBS) (C7) => stereodetermining step governed by hybridization of C7



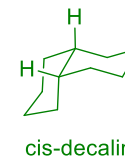
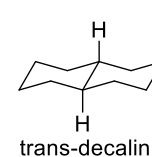
- Access to **trans-decalin**

Inoue, *J. Org. Chem.* **2021**, *86*, 6869

Sn radical used for halo-abstraction to generate stable tertiary C-centered radical

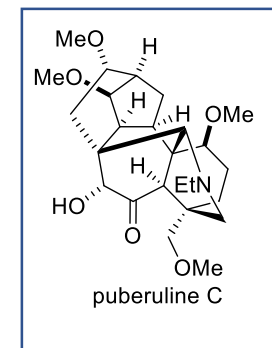
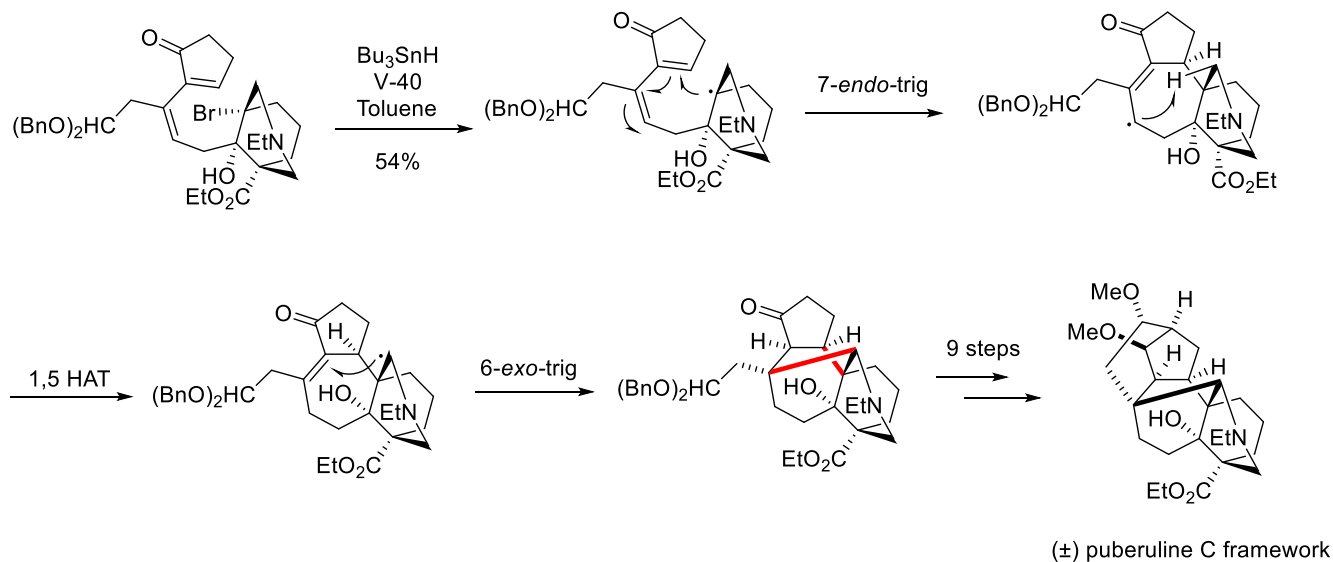


- First 6-endo occurs from bottom face of the pseudo-boat form due to sp^2 hybridized carbon atom next to double bond ($\text{C}=\text{O}$) (C9) => stereodetermining step governed by hybridization of C7
- Notable access to *thermodynamically non-favoured* **cis-decalin**



Inoue, *J. Org. Chem.* **2021**, *86*, 6869

Sn radical used for halo-abstraction to generate stable tertiary C-centered radical

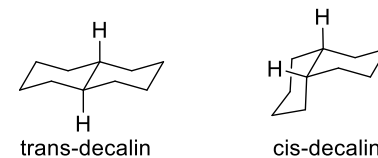
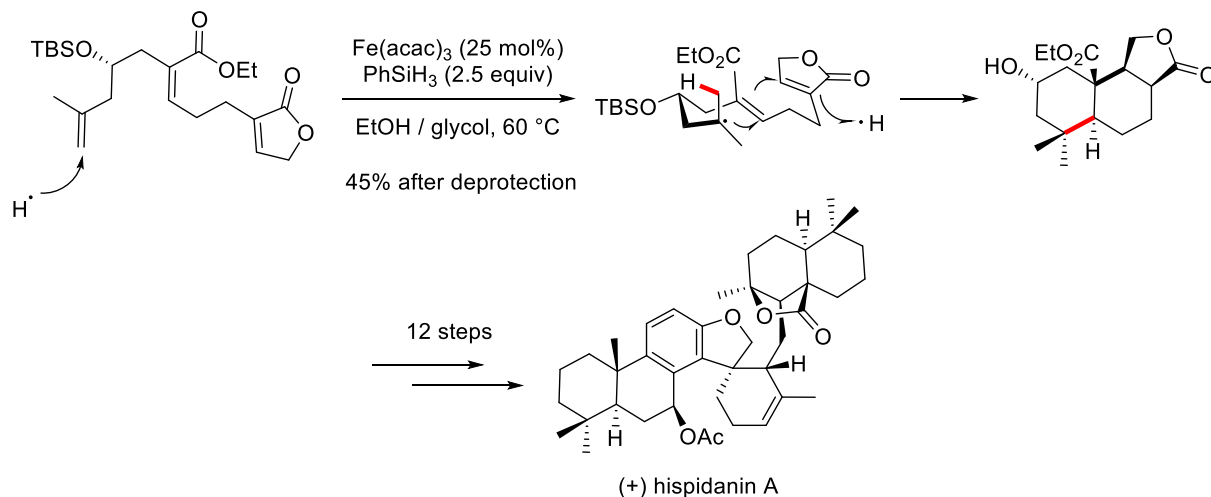


- First synthesis of the hexacyclic framework of Puberuline C
- Challenging 7-endo trig cyclization (**DFT** : optimal SOMO/LUMO interaction)

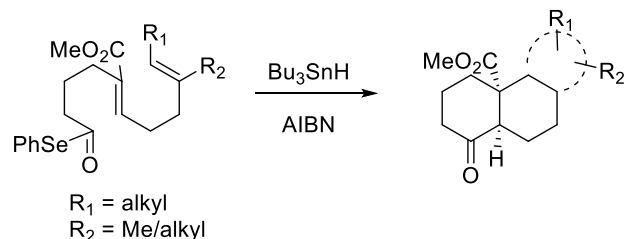
Inoue, *Chem. Sci.* **2016**, *7*, 4372

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 - aldehydes / ketones
 - alkyls
 - **alkenes**
 - alkynes
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C-Centered radical : alkenes

Fe-mediated hydrogen radical generation and addition on alkene radical acceptor

Trans-decalin favored thanks to mismatched radical/acceptor philicity. Slow radical addition favours thermodynamic product.



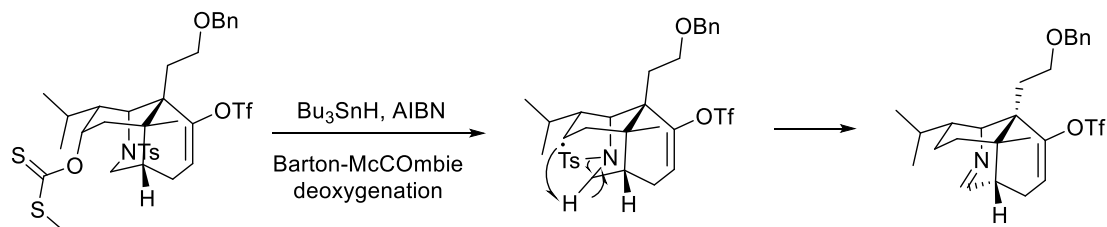
Cis-decalin isomer observed due to steric repulsion with ester group.

Liu, *Angew. Chem. Int. Ed.* **2017**, *56*, 5849

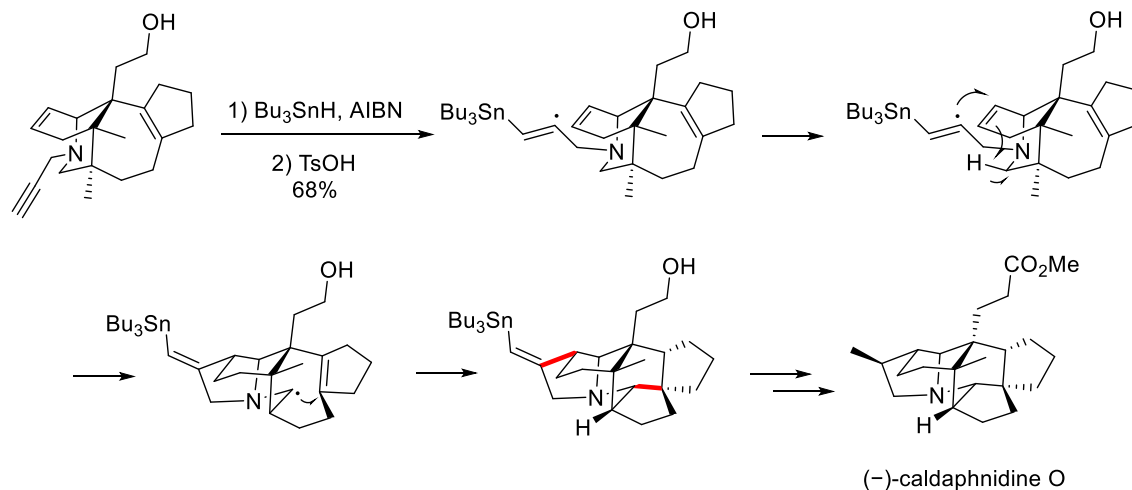
Pattenden, *J. Chem. Soc., Perkin Trans. 1*, **2000**, 3522

- Intro – radical generation
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 - alkyne
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 - N-amidyl radical

An enyne radical cyclization triggering 1,5 HAT



Unexpected Tosyl deprotection in Barton – McCombie deoxygenation conditions triggered by 1,5 HAT during the synthesis of Dapholdhamine B

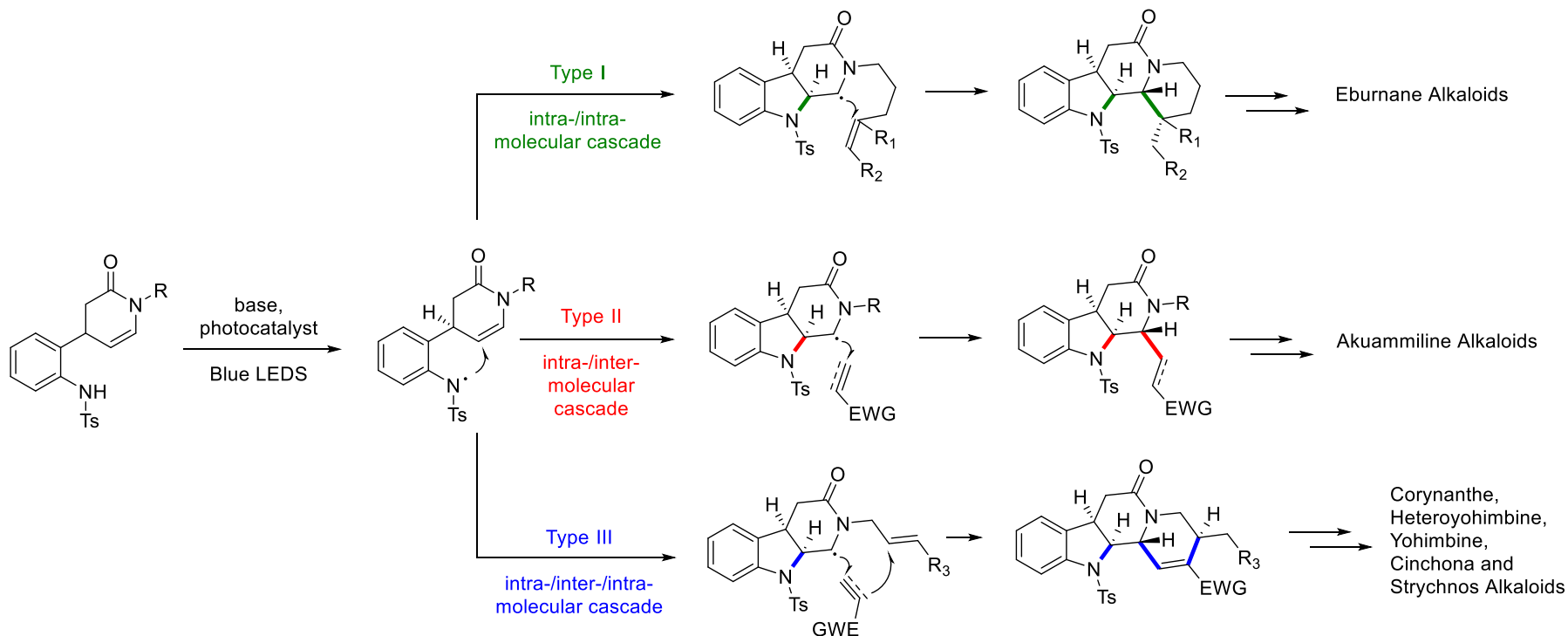
Sn radical addition on alkyne radical acceptor

Xu, *J. Am. Chem. Soc.* **2019**, *141*, 13043

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 - alkyne
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 - N-amidyl radical

N-Centered radical : aminyl

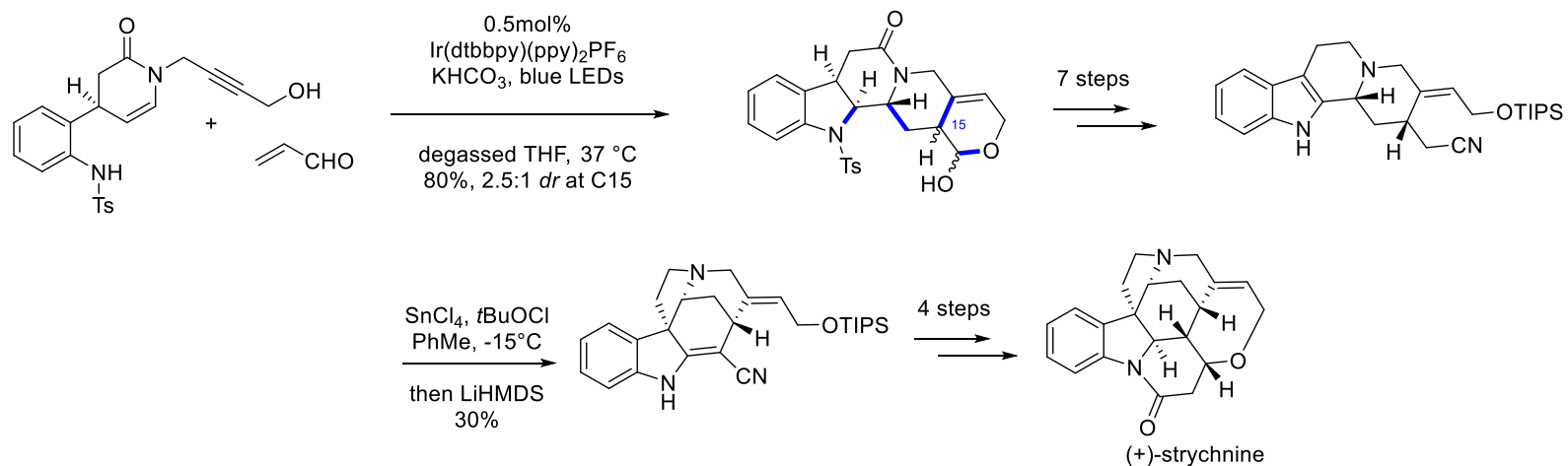
Ir photocatalytic single electron oxidation of N anion generated from basic deprotonation



First use of photocatalytic radical generation for natural product synthesis

Qin, *Acc. Chem. Res.* **2019**, *52*, 1877

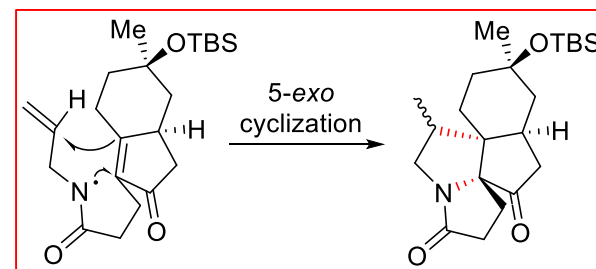
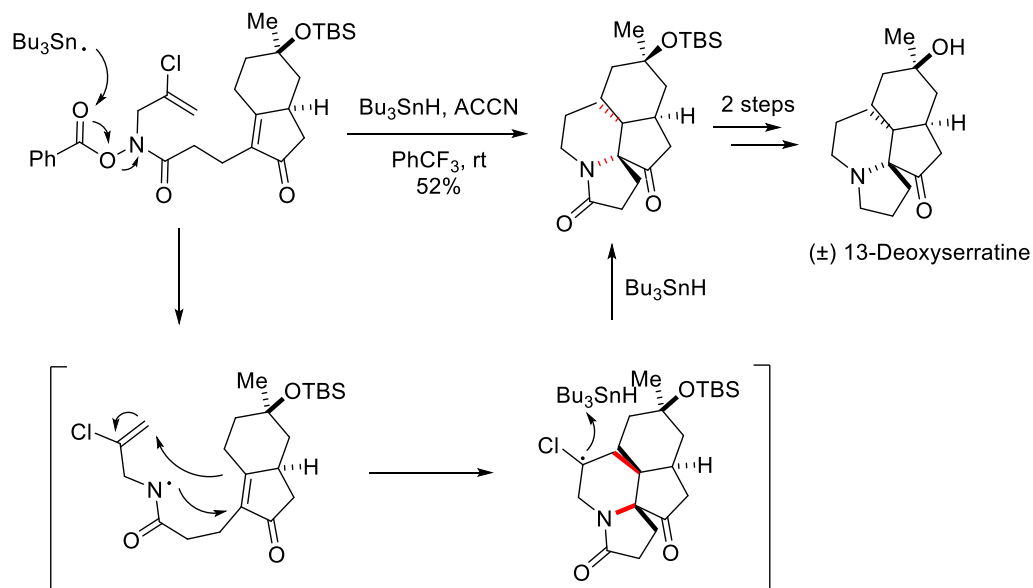
Strychnos Alkaloids : (+)-strychnine



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 - N-amidyl radical

N-Centered radical : amidyl

Sn radical used for benzoyl-abstraction to generate amidyl radical



Observed cyclization product when using hydrogen substituted precursors

The chlorine substituent is introduced to direct 6-endo versus 5-exo cyclization

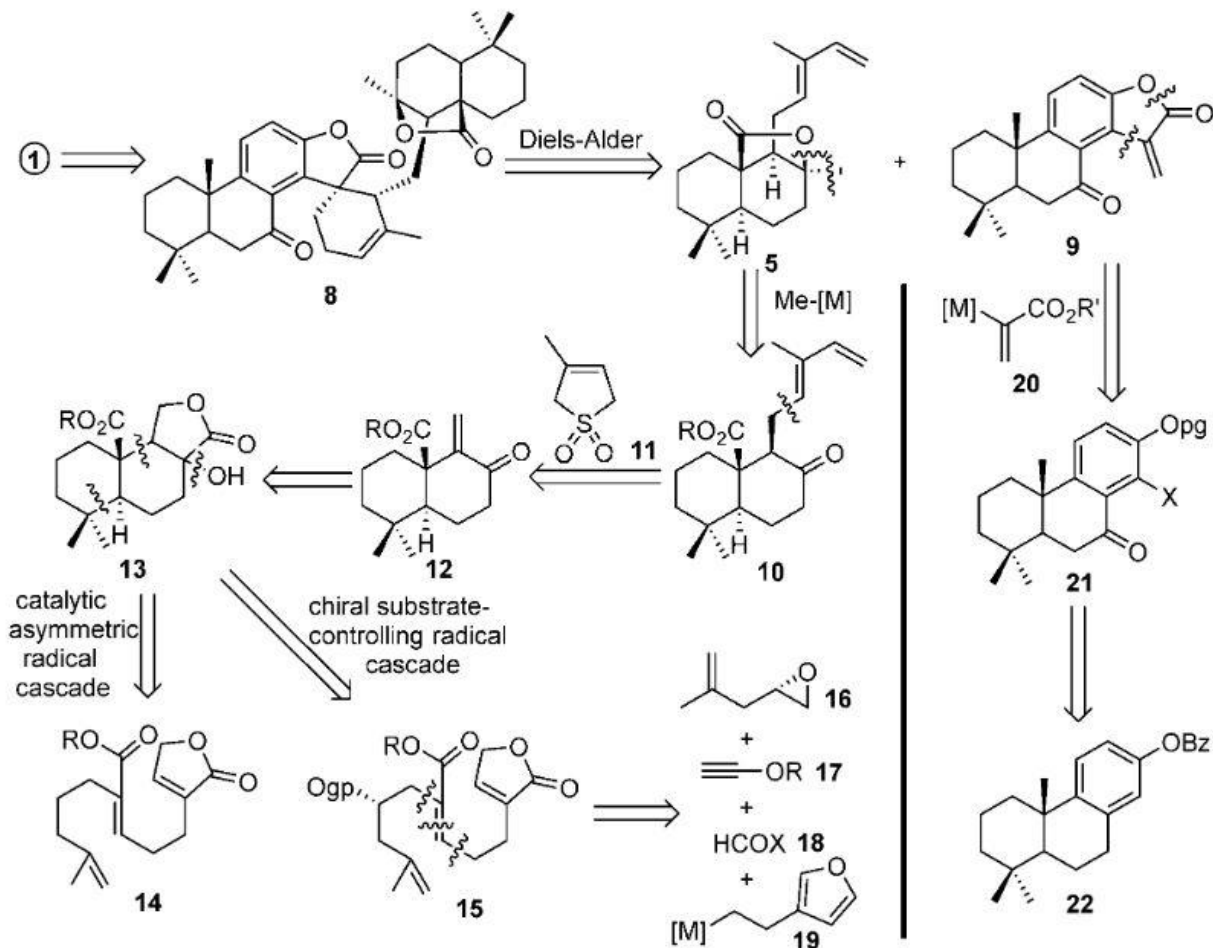
Cascade radical polycyclization reactions

- Well implemented in nowadays total synthesis
- Ultra short access to complex frameworks
- Radicals propagate until being “stopped”

=> “infinite” potential but also very **challenging cascade design**

Thank you all for your attention !

C-Centered radical : alkenes



Scheme 1. Retrosynthetic analysis of hispidanin A.